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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/665,111	09/16/2003	Dolores Schendel	1406/468	6128

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JENKINS, WILSON, TAYLOR & HUNT, P. A.
Suite 1200 UNIVERSITY TOWER
3100 TOWER BLVD.,
DURHAM, NC 27707

EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/665,111	SCHENDEL ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-30 and 33-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-25,27,28,30,32-34,36-40 and 43-46* is/are rejected.

7)☐ Claim(s) *26, 29, 35, 41, 42* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 23 and 33 have been amended. Claims 23-30, and 33-46 are pending and under consideration.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The rejection of claims 23, 27, 28, 30, 32, 33, 34, 37-40 and 43-46 under 35 U.S.C. 102(e) as being anticipated by Ohno (U.S. Appn 2002/0168351) is maintained for reasons of record.

Ohno disclose a method for treating cancer comprising the administration of chimeric cells comprising tumor cells fused to autologous dendritic cells [023, , 025]. Ohno discloses that the cancers which can be treated are cancer is selected from the group consisting of renal cell carcinoma, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchiogenic carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma,

pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, leukemias, acute lymphocytic leukemia, acute myelocytic leukemia; chronic leukemia, polycythemia vera, lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, and heavy chain disease [0036], which fulfill the specific embodiments of claim 28, 34, 43 and 44. Ohno discloses that CTL in the patient receiving the fusions cells are stimulated by the presentation of mucin antigens or Her-2/neu epitopes [130] which fulfills the specific embodiments of claims 45 and 46. Ohno discloses intravenous, subcutaneous and intramuscular routes of administration of the fusion cells [0145] which fulfills the specific embodiment of claim 37. Ohno meets the limitations of claims requiring RNA from tumor cells which has been introduced in recombinant form because the expression of the tumor cell peptides by the fused dendritic cell is a recombinant form of expression of the tumor cell RNA encoding the peptides. because the tumor cell peptides are now being expressed by the dendritic cell due to the fusion of the two cell types, and thus the limitation of "recombinant" is met. further, it would be inherent in the fusion cells of Ohno that proteins or peptides which are over expressed in the tumor cells would be expressed by the dendritic cell fusion via the over expressed RNA present in the tumor cell of the fusion.

The rejection of claims 23, 25, 27, 28, 30, 32, 33, 34, 36-40 and 43-46 under 35 U.S.C. 103(a) as being unpatentable over Ohno (U.S. Appn 2002/0168351) in view of Nair et al (WO 97/41210, cited in a previous Office action) is maintained for reasons of record.

Ohno teaches fusions of autologous dendritic cells with tumor cells for the expression of the tumor cell peptides by the dendritic cell. Ohno does not teach autologous dendritic cells which are transfected with nucleic acids encoding tumor cell peptides to produce the expression of said peptides by the autologous dendritic cells.

Nair et al teach method for the loading of dendritic cells by introduction of a tumor associated RNA which is unfractionated or cDNA made by PCR (page 3, lines 13-19). Nair et al disclose that the method offers advantages in that there is no need to identify specific tumor rejection antigens and an immune response to unfractionated RNA or cDNA made therefrom elicits immune responses to several tumor antigens reducing the likelihood of escape mutants and extends the use of active immunotherapy to the treatment of cancers for which specific

tumor antigens have not yet been identified which is the vast majority of cancers (page 9, lines 21-35). Nair et al teach a method for treating cancer comprising directly administering the loaded dendritic cells to a patient suffering from cancer (claims 51-53).

It would have been prima facie obvious at the time the claimed invention was made to substitute the RNA or cDNA transfected dendritic cells to a patient having cancer. One of skill in the art would have been motivated to do so by the teachings of Nair et l regarding the improvements associated with using unfractionated RNA for the loading of dendritic cells, and the administration the loaded dendritic cells as part of the immunotherapy as taught by Nair et al.

The rejection of claims 23-25, 27, 28, 30, 32, 33, 34, 36-46 under 35 U.S.C. 103(a) as being unpatentable over Ohno (U.S. Appn 2002/0168351) and Nair et al (WO 97/41210) as applied to claims 23, 25, 27, 28, 30, 32, 33, 34, 36-40 and 43-46 above, and further in view of Storkus et al (U.S. 6,077,519, cited in a previous Office action) is maintained for reasons of record.

Claims 24 and 41 embody the method of claim 23 wherein proteins, peptide, RNA, DNA or cDNA from several different tumor cell lines are introduced into the HLA-haploidentical APC. Claim 42 embodies the method of claim 41 wherein pooled cDNA from two or three different tumor cell lines is introduced.

The combination of Ohno and Nair et al render obvious the instant invention regarding the loading of haploidentical APC with unfractionated RNA or cDNA made therefrom from tumor tissue from the patient. The combination does not teach or suggest the use of multiple tumor cell lines as a source of peptides, RNA or cDNA for loading or pulsing dendritic cells.

Storkus et al teach that dendritic cells can be pulsed with HLA-attached allogeneic tumor cell lines as an alternative to acid eluted peptides from the patients tumor cells (column 12, lines 21-32). Storkus et al teach the administration of pulsed dendritic cells by intravenous routes (column 35, lines 53-60). Storkus et al teach that the invention be applied to treat colon, squamous, gastric, breast, prostate, lung, cervical and ovarian carcinomas. It is noted that prostate carcinomas would inherently express prostate specific membrane antigen.

It would have been prima facie obvious at the time the claimed invention was made to

use pooled tumor cell acid eluted peptides or RNA or cDNA for pulsing or loading the dendritic cells used in the methods rendered obvious by the combination of Greenman et al and Nair et al. One of skill in the art would have been motivated to do so by the suggestion of Storkus et al that cell lines can be used as a source of tumor specific antigen peptides. One of skill in the art would have been motivated to look to this source in the event that no tumor material from the patient was available or insufficient. One of skill in the art would have been motivated to used pooled acid eluted peptides or unfractionated RNA or unfractionated cDNA from several different tumor cell lines because of the teachings of Nair et al regard tumor escape mechanisms. One of skill in the art would understand that providing a multitude of antigens to the dendritic cell would compensate for the ability of a tumor to down regulate an antigen and escape immune surveillance. The more tumor specific antigens which can be expressed by the activated dendritic cells, the more populations of activated T cells will be available for recognition of tumor cells. Further, because the method is taught by Storkus et al to extend to the treatment of prostate cancer, the unfractionated RNA, cDNA made therefrom would inherently include prostate specific membrane antigen, PSMA, thus fulfilling the limitations of claims 45 and 46.

The rejection of claims 23, 27, 28, 30, 32, 33, 34, 37-40 and 43-46 under 35 U.S.C. 103(a) as being unpatentable over Ohno (U.S. Appn 2002/0168351) is maintained for reasons of record.

Claims 26 and 35 embody the methods of claim 23 and 33 respectively, wherein antigen-presenting cells of two different haploidentical individuals are used.

Ohno teaches using antigen-presenting cells which are autologous. Ohno does not teach dendritic cells from haploidentical individuals.

It would have been prima facie obvious to use a mixture of haploidentical dendritic cells and autologous dendritic cells in the event that there was a deficiency in the quantity of dendritic cells obtained from the patient. One of skill in the art would have been motivated to provide more dendritic cells in place of the autologous dendritic cells in order to obtain enough of the dendritic cell-tumor cell chimeric cells with which to treat the patient.

Applicant argues that the disclosure of Ohno et al cannot anticipate or render obvious the

instant claims because Ohno et al discloses autologous antigen presenting cells rather than the haploidentical antigen presenting cells required by the instant claims. Applicant argues that autologous cells are mutually exclusive of haploidentical cells. Applicant reasons that in order for the APC to be HLA-haploidentical , the donor of the APC must be related to the patient and must have inherited the same HLA gene complex on one of their chromosomes 6, but not on the other chromosome 6, resulting in a donor with one of the two copies of HLA on chromosome 6 being generally identical to those of the patient. This has been considered but not found persuasive. The Dictionary of Immunology (Third Edition, Herbert et al, Ed.s, 1985) defines haplotype as "Literally half-a-genotype; refers to the complete set of MHC loci and the closely associated loci inherited" from one parent. Each somatic cell will have two haplotypes, one paternally derived and one maternally derived. Thus and autologous cell from a patient will have two identical haplotypes to said patient.

Claims 26, 29, 35, 41 and 42 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

All other rejections and objections as set forth or maintained in the previous Office action are withdrawn in light of applicant's amendments.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Karen A Canella/
Primary Examiner, Art Unit 1643